UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: [illegible]
Washington, [illegible]
www.uspto.gov

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/975,123	10/09/2001	Susan M. Freier	RTS-0253	3629

[illegible] 05/29/2002

Jane Massey Licata
Licata & Tyrrell, P.C.
66 East Main Street
Marlton, NJ 08053

EXAMINER
ZARA, JANE J

ART UNIT	PAPER NUMBER
[illegible]	4

DATE MAILED: 05/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/975,123	FREIER, SUSAN M
	Examiner	Art Unit
	Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____

2a)☐ This action is **FINAL** 2b)☒ This action is non-final

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1☐ Certified copies of the priority documents have been received.

2☐ Certified copies of the priority documents have been received in Application No. _____

3☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

DETAILED ACTION

Claims 1-20 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro targeting and inhibition of human insulin like growth factor binding protein 5 (hIGF-BP5) comprising the administration of antisense oligonucleotides in vitro, does not reasonably provide enablement for the in vivo targeting and inhibition of any and/or all nucleic acids encoding IGF-BP5 and further whereby treatment and prophylactic effects are provided for any and/or all diseases or conditions which are associated with IGF-BP5 in any animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of inhibiting the expression of (any form of) IGF-BP5 comprising the administration, in vitro or in vivo and by any means, of antisense oligonucleotides between 8 and 50 nucleobases in length which target IGF-BP5. The claims are also drawn to methods of treating or preventing any condition, disease or disorder associated

with IGF-BP5 in an animal comprising the administration of antisense oligonucleotides between 8 and 50 nucleobases in length which target IGF-BP5.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2).

Tamm et al, in a review article discussing the therapeutic potential of antisense in treating

oligonucleotides in the field of oncology, is still missing." (see especially pages 490-493 for a summary of various clinical trials in process using antisense). Additionally, Agrawal et al point to various factors contributing to the unpredictability of antisense therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80).

Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

Some success has been reported regarding the use of antisense in targeting IGF-BP5 in an androgen dependent Shionogi tumor model in mice. Miyake et al have found that the intraperitoneal administration of an antisense oligonucleotide 16 nucleobases in length and

transplanted LNCaP tumor cells (which tumor cells had been transfected in vitro with a plasmid encoding mIGF-BP5 prior to their transplantation into mice) (see Miyake et al, International J. of Urology, Vol. 8, pages 337-349, especially at page 346, figure 9). While such findings provide hope for effective treatment methods using antisense strategies, the ability to predict the success of antisense in reaching a desired target cell, in inhibiting a desired target gene and in providing treatment effects for a given disease or condition are still highly unpredictable endeavors.

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting the expression of any and/or all forms of IGF-BP5, in vitro or in vivo, comprising the administration of antisense. Applicants have not provided guidance toward a method of treating or preventing any disease or condition associated with the expression of IGF-BP5 in an organism comprising the administration of antisense.

The specification teaches the in vitro inhibition of expression of hIGF-BP5 encoded by SEQ ID NO: 3 comprising the administration of antisense which target a nucleic acid encoded by SEQ ID NO: 3, as well as comprising the administration of antisense which target 5' UTR regions encoded by SEQ ID NO: 10, intron regions encoded within SEQ ID NO: 11, and 3' UTR region encoded within SEQ ID NO: 12, all as indicated in Table 1 of the instant specification (pages 84-85). The specification fails to teach the treatment or prevention of any and/or all conditions or diseases associated with IGF-BP5 in any organism comprising the administration of

on its face the examples given in the specification of the in vitro inhibition of expression of hIGF-BP5 as being correlative or representative of the successful inhibition of expression of any and/or all nucleic acids encoding any and/or all forms of IGF-BP5 in vitro or in vivo, and further whereby treatment or prophylactic effects are provided for any disease or condition associated with the expression of IGF-BP5 in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the efficacy of antisense in treating any and/or all diseases or conditions associated with the target gene encoding IGF-BP5 in an organism. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to methods of inhibiting the expression of (any form of) IGF-BP5 comprising the administration, in vitro or in vivo and by any means, of antisense oligonucleotides between 8 and 50 nucleobases in length which target IGF-BP5. The claims are also drawn to methods of treating or preventing any condition or disorder associated with IGF-BP5 in an animal comprising the administration of antisense oligonucleotides between 8 and 50 nucleobases in length which target IGF-BP5. The quantity of experimentation required to practice the invention as claimed would require the *de novo*

cells and /or tissues harboring the target gene IGF-BP5, whereby IGF-BP5 expression is inhibited in vitro and in vivo, and further whereby treatment and/or prophylactic effects are provided for any and/or all diseases or conditions associated with IGF-BP5 in any organism. Since the specification fails to provide any particular guidance for the successful inhibition of expression of any and/or all forms of IGF-BP5 in vitro or in vivo, nor for the successful treatment or prevention of any and/or all diseases or conditions associated with IGF-BP5 in an organism, and since determination of these factors for a particular disease or condition is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 5, 11, 12, 14, 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Huynh et al.

Huynh et al teach antisense oligonucleotides between 8 and 50 nucleobases that

expression of IGF-BP5 in cells in vitro, and which antisense oligonucleotides are in compositions comprising a pharmaceutically acceptable diluent, and which antisense oligonucleotides comprise phorphorothioate internucleotide linkages (see entire document, especially the abstract on page 1501; figure 5 and the first full paragraph on page 1505).

Claims 1-5, 11-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Melone et al.

Melone et al teach antisense oligonucleotides between 8 and 50 nucleobases that specifically target an active site on nucleic acid molecule encoding IGF-BP5, and inhibit the expression of IGF-BP5 in cells in vitro, and which antisense oligonucleotides are in compositions comprising a pharmaceutically acceptable diluent and a colloidal dispersion, and which antisense oligonucleotides comprise phorphorothioate internucleotide linkages (See entire document, especially the first full paragraph on page 146, which oligonucleotide aligns with SEQ ID NO: 13 of the instant application; also see especially figures 8 and 9 on page 151).

Claims 1, 2, 4, 5, 11, 12, 14-19 are rejected under 35 U.S.C. 102(a) as being anticipated by Miyake et al.

Miyake et al (International J. Urology, Vol. 8, pages 337-349) teach the intraperitoneal administration of compositions comprising an antisense oligonucleotide between 8 and 50

and in tumor cells in mice (a prostate related mouse model system), and which compositions also comprise a pharmaceutically compatible diluent, and which antisense comprises phosphorothioate internucleotide linkages, whereby tumor reduction is observed following the administration of antisense to the mice (see especially the text on pages 337-338; figure 2 on page 339; text on page 344; figure 9b on page 346. Also see accompanying Miyake rejection directly below for a description of the antisense oligonucleotides used in this in vivo study).

Claims 1, 2, 4, 5, 11-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Miyake et al.

Miyake et al (Cancer Res. Vol. 60, pages 3058-3064) teach the in vitro administration of compositions comprising antisense oligonucleotides which specifically target an active site on the nucleic acid encoding mIGF-BP5, and inhibit the expression of the nucleic acid encoding mIGF-BP5 in target cells in vitro, and which compositions further comprise a colloidal dispersion and a pharmaceutical compatible diluent, and which antisense comprise phosphorothioate internucleotide linkages. Miyake et al teach the intraperitoneal administration of compositions comprising an antisense oligonucleotide between 8 and 50 nucleobases in length which specifically targets mIGF-BP5 and inhibits its expression in vitro and in tumor cells in mice (a prostate related mouse model system), and which composition also comprises a pharmaceutically compatible diluent, and which antisense comprises phosphorothioate

antisense to the mice (see abstract on page 3058; fourth and fifth full paragraphs on page 3059; text and figures 3, 4, 5, 6 on pages 3060-3063).

Claims 1-5, 11-19 are rejected under 35 U.S.C. 102(a) as being anticipated by Miyake et al.

Miyake et al (WO 01/05435 A2) teach the in vitro administration of compositions comprising antisense oligonucleotides which specifically target an active site on the nucleic acid encoding mIGF-BP5, and inhibit the expression of the nucleic acid encoding mIGF-BP5 in target cells in vitro, and which compositions further comprise a colloidal dispersion and a pharmaceutical compatible diluent, and which antisense comprise phosphorothioate internucleotide linkages. Miyake et al teach the intraperitoneal administration of compositions comprising an antisense oligonucleotide between 8 and 50 nucleobases in length which specifically targets mIGF-BP5 and inhibits its expression in vitro and in tumor cells in mice (a prostate related mouse model system), and which composition also comprises a pharmaceutically compatible diluent, and which antisense comprises phosphorothioate internucleotide linkages, whereby tumor reduction is observed following the administration of antisense to the mice (See entire document, especially figures 1-6, 8-10; also see accompanying nucleic acid sequence alignments between SEQ ID NO: 14 and AAA91253 of Miyake; SEQ. ID NO: 16 and AAA91241 of Miyake; SEQ ID NO: 17 and AAA91240 of Miyake; SEQ ID NO: 19 and

AAA91239 of Miyake; SEQ ID NO: 21 and AAA91202 of Miyake; SEQ Id NO: 25 and AAA91203 of Miyake).

Claims 1, 2, 3, 11, 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Pavco et al.

Pavco et al teach antisense oligonucleotides which target and specifically hybridize with an active site of a nucleic acid encoding IGF-BP5 and inhibit the expression of a nucleic acid encoding IGF-BP5 in vitro (see the accompanying nucleic acid sequence alignments between SEQ ID NO: 31 and AAA23134 of Pavco; SEQ ID NO: 32 and AAA23417 of Pavco).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyake et al, Pavco et al, Huynh et al and Melone et al as applied to claims 1-5 and 11-15 above, and further in view of McKay et al insofar as the claims are drawn to compositions and methods for targeting and inhibiting the expression of IGF-BP5 in vitro comprising the administration of antisense

internucleotide linkage modifications such as phorothioate linkages, nucleobase modifications such as 5-methyl cytosines, and sugar modifications such as 2'-O-methoxyethyl sugars, or optionally comprise chimeric structures, and which compositions comprise a pharmaceutically compatible diluent and a colloidal dispersion, and which antisense specifically target an active site on a nucleic acid molecule encoding IGF-BP5 in vitro..

Miyake et al (3 references cited above), Pavco et al, Huynh et al and Melone et al are relied upon as cited in the 102 rejections above.

The primary references do not teach the incorporation of sugar or nucleobase modifications, or chimeric constructs into antisense oligonucleotides.

McKay et al teach the incorporation of modified nucleobases such as 5-methyl cytosines and modified sugar residues such as 2'-O-methoxyethyl sugar moieties and chimeric constructs into antisense oligonucleotides (See especially col. 6-11).

It would have been obvious to one of ordinary skill in the art to incorporate various nucleobase and sugar modifications into antisense oligonucleotides, as well as chimeric constructs into antisense oligonucleotides because such modifications had been taught previously by McKay et al. One of ordinary skill in the art would have been motivated to incorporate such modifications, including 5-methyl cytosines and 2'-O-methoxyethyl sugars, as well and chimeric structures into antisense because these modifications had been known to enhance target binding, cellular uptake and stability of antisense oligonucleotides. One of ordinary skill in the art would

and stability of antisense oligonucleotides which are targeted to IGF-BP5, because such modifications have been incorporated into antisense oligonucleotides with varying sequences, and the incorporation of such modifications would have been a routine endeavor for one of ordinary skill in the art at the time the invention was made.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TC/1600

JZ